

CLAIMS:

1. A method for diagnosis of Alzheimer's disease
in a human subject which comprises screening for the
5 presence of a cell cycle regulatory defect at the G1/S
phase transition in non-neuronal cells of the human
subject

2. A method according to claim 1 wherein a
10 reduction in the effectiveness of the checkpoint
control at the G1/S transition is taken as an
indication that the subject has Alzheimer's disease.

3. A method according to claim 1 or claim 2
15 wherein screening for the presence of a cell cycle
regulatory defect at the G1/S phase transition is
carried out by:
inducing cell division in the non-neuronal cells and
testing the responsiveness of the cells to a cell
20 division inhibitor substance, wherein a reduced
responsiveness to the cell division inhibitor
substance in cells from the subject, as compared to
control cells not having a cell cycle regulatory
defect at the G1/S phase transition, is taken as in
25 indication of the presence of a cell cycle regulatory
defect at the G1/S phase transition.

4. A method according to claim 3 wherein the
cell division inhibitor substance is a specific G1
30 inhibitor.

5. A method according to claim 1 or claim 2
wherein screening for the presence of a cell cycle
regulatory defect at the G1/S phase transition is
35 carried out by:
inducing cell division in the non-neuronal cells and
testing the responsiveness of the cells to a stimulus

that induces cell cycle arrest, wherein a reduced
responsiveness to said stimulus in cells from the
subject, as compared to control cells not having a
cell cycle regulatory defect at the G1/S phase
5 transition, is taken as an indication of the presence
of a cell cycle regulatory defect at the G1/S phase
transition.

6. A method according to claim 5 wherein the
10 stimulus that induces cell cycle arrest is selected
from oxidative stress, ionising radiation, hypoxia, or
UV radiation.

7. A method according to any one of claims 3 to
15 6 wherein the responsiveness of the cells to the cell
division inhibitor substance or stimulus that induces
cell cycle arrest is tested by a cell proliferation
assay, relatively higher proliferative activity in
cells from the subject, as compared to control cells
20 not having a cell cycle regulatory defect at the G1/S
phase transition, following treatment with the cell
division inhibitor or stimulus that induces cell cycle
arrest being taken as an indication of the presence of
a cell cycle regulatory defect at the G1/S phase
25 transition.

8. A method according to any one of claims 3 to
6 wherein the responsiveness of the cells to the cell
division inhibitor substance or stimulus that induces
30 cell cycle arrest is tested by calculating the
relative lengthening of the G1 phase of the cell cycle
in cells from the subject, a reduced relative
lengthening of the G1 phase in the presence of the
cell division inhibitor substance or stimulus in said
35 cells, as compared to control cells not having a cell
cycle regulatory defect at the G1/S phase transition,
being taken as an indication of a cell cycle

regulatory defect at the G1/S phase transition.

9. A method according to any one of claims 3 to 6 wherein the responsiveness of the cells to the cell division inhibitor substance or stimulus that induces cell cycle arrest is tested by analysis of expression of a cell cycle regulatory protein or an mRNA encoding a cell cycle regulatory protein.

10. A method as claimed in claim 9 wherein the cell cycle regulatory protein is selected from the group consisting of CDKN3, p15ink4B, p16ink4A, p19ink4D, p27kip1, p21cip1, p57kip2 and TP53.

11. A method according to claim 5 wherein the stimulus that induces cell cycle arrest is DNA damage and the responsiveness of the cells to the cell this stimulus is tested by analysis of expression of a DNA damage-response element.

12. A method according to claim 11 wherein the DNA damage-response element is selected from the group consisting of TP53, Gadd34, Gadd45A, Gadd45B, Gadd45G, Gadd153 and PCNA.

13. A method according to any one of claims 3 to 6 wherein the responsiveness of the cells to the cell division inhibitor substance or stimulus that induces cell cycle arrest is tested by assessment of cell viability or cell death, wherein increased cell survival or a reduced degree of cell death in said cells, as compared to control cells not having a cell cycle regulatory defect at the G1/S phase transition, following exposure to the cell division inhibitor or other stimulus that induces cell cycle arrest is taken as an indication of the presence of a cell cycle regulatory defect at the G1/S phase transition.

14. A method according to any one of claims 3 to 6 wherein the responsiveness of the cells to the cell division inhibitor substance or stimulus which elicits cell cycle arrest is tested by analysis of expression of a cell death related protein or an mRNA encoding a cell death related protein.

15. A method according to claim 14 wherein the cell death related protein is a member of the bcl-2 family of proteins.

16. A method according to any one of claims 3 to 6 wherein the responsiveness of the cells to the cell division inhibitor substance or stimulus which elicits cell cycle arrest is tested by assessment of DNA content of the cells with or without cell cycle analysis.

17. A method according to any one of claims 1 to 16 wherein the non-neuronal cells are lymphocytes.

18. A method according to any one of claims 1 to 17 for diagnosis of sporadic Alzheimer's disease.

19. A method for use in diagnosis of Alzheimer's disease in a human subject which comprises screening for the presence in the genome of said subject of at least one mutation or allelic variant in a cell cycle regulatory gene, wherein the presence of a mutation or allelic variant in a cell cycle regulatory gene is taken as an indication of Alzheimer's disease.

20. A method of determining any genetic basis for Alzheimer's disease in a human subject, which comprises screening the genome of said subject for the presence of mutations or allelic variants in a cell cycle regulatory gene.

21. A method of screening a human subject for pre-disposition to Alzheimer's disease which comprises screening for the presence in the genome of said subject of at least one mutation or allelic variant in a cell cycle regulatory gene.

22. A method according to any one of claims 19 to 21 which comprises screening for the presence of mutations or allelic variants in at least one gene selected from: CDKN3, p15ink4B, p16ink4A, p19ink4D, p27kip1, p21cip1, p57kip2 and TP53.

23. A method according to claim 22 which comprises genotyping for one or more of the p21E2 A/B polymorphism, the p57E2A A/B polymorphism, or the p57E2B A/B polymorphism.

24. A method for use in diagnosis of Alzheimer's disease in a human subject which comprises screening for the presence in the genome of said subject of at least one mutation or allelic variant in a gene encoding a DNA repair enzyme, wherein the presence of a mutation or allelic variant in such a gene is taken as an indication of Alzheimer's disease.

25. A method of determining any genetic basis for Alzheimer's disease in a human subject, which comprises screening the genome of said subject for the presence of mutations or allelic variants in a gene encoding a DNA repair enzyme.

26. A method of screening a human subject for pre-disposition to Alzheimer's disease which comprises screening for the presence in the genome of said subject of at least one mutation or allelic variant in a gene encoding a DNA repair enzyme.

27. A method according to any one of claims 24
to 26 which comprises screening for the presence of
mutations or allelic variants in at least one gene
selected from: Ku70, Ku80, Ku86, NDHII, BLM, RECQL,
5 RECQL4 and RECQL5.

28. A method of identifying compounds having
potential pharmacological activity in the treatment of
Alzheimer's disease, which method comprises steps of:
10 analysing the regulation of the G1/S transition
in non-neuronal cells, which cells exhibit a cell
cycle regulatory defect at the G1/S phase transition,
in the presence and absence of a test compound,
wherein a test compound which results in correction of
15 the regulatory defect at the G1/S transition in said
cells is identified as having potential
pharmacological activity in the treatment of
Alzheimer's disease.

29. A method of determining whether a
pharmacological agent is likely to be of benefit in
the treatment of Alzheimer's disease in a particular
human individual, which method comprises:
25 analysing the regulation of the G1/S transition
in cells from said individual, which cells are non-
neuronal cells that exhibit a cell cycle regulatory
defect at the G1/S phase transition, in the presence
and absence of the pharmacological agent, wherein a
pharmacological agent which results in correction of
30 the regulatory defect at the G1/S transition in said
cells is identified as likely to be of benefit in the
treatment of Alzheimer's disease in said individual.